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PUBLIC HEALTH REPORTS

VOL. 37

MAY 12, 1922

No. 19

CARBON TETRACHLORIDE.

A Drug Proposed for the Removal of Hookworms, with Special Reference to its Toxicity for Monkeys when Given by Stomach Tube in Repeated Doses.

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Hall¹ recently published in the *Journal of the American Medical Association* an account of experimental work in which he used carbon tetrachloride as an anthelmintic for dogs, and found it highly effective against hookworms. With a large series of dogs he was able to secure expulsion of all the hookworms following a dose by stomach of about 0.3 gm. of the drug per kilogram of the dog's weight. This is the most favorable result Hall has been able to obtain after treating hundreds of dogs with many different anthelmintics, including those in best repute.

Hall found that carbon tetrachloride was not only the most effective drug therapeutically that he had tried as an anthelmintic for hookworms but was also the least toxic of any of the active vermifuges tried. Without any evidence of discomfort, dogs withstood 1.5 c. c. per kg., or five times the effective dose of 0.3 c. c. per kg.

As a further proof of his belief in the low toxicity of carbon tetrachloride, Hall tried the drug on himself, taking the dose of 3 c. c. This is the average dose given a dog, and Hall regards the doses required for dog and man as being about the same. He experienced no unpleasant symptoms. Hall also gave the results of some experiments on monkeys carried out jointly with Shillinger and Lake, in which doses two to five times the dose indicated for man, or 6 to 15 c. c., were given to animals weighing 2.5 to 3.5 kg. The largest dose was 6 c. c. per kg., or, on the basis of cubic centimeters of drug per kilogram of animal's weight, over one hundred times the dose indicated for man. These monkeys showed no definite symptoms of intoxication and, after being held under observation for a month or longer, were used in experiments in poliomyelitis, which usually causes marked changes only in the central nervous system. Post-mortem examination after their death from the poliomyelitis virus

¹ Hall, M. C.: The use of carbon tetrachloride for the removal of hookworms. *Jour. Am. Med. Assn.* vol. 77, No. 21, Nov. 19, 1921, pp. 1641-1643.

showed no gross changes in the liver or other viscera. Microscopic examinations were not made.

More recently Allen ² reports the treatment of about 400 fur foxes, for removal of hookworms, with carbon tetrachloride with very satisfactory results.

The experiments here recorded were carried out at the suggestion of Dr. G. W. McCoy, who believed it might be essential to use repeated doses of carbon tetrachloride in man, and hence it would be important to know first the results of repeated doses in monkeys.

Four monkeys were used. The weights of the monkeys were from 2,210 to 2,630 grams. At each dosage monkey No. 1 received, by stomach tube, 1 c. c.; monkey No. 2 received 2 c. c.; monkey No. 3 received 3 c. c.; and monkey No. 4 received 5 c. c. of carbon tetrachloride. These doses were administered on January 24, 27, 30, February 2, 4, 6, 8, 11, 14, 16, 18, and 20, 1922.

On February 23, monkey No. 4, which had received a total of 60 c. c. during a period of 30 days and appeared to be in good health, was inoculated subdurally with monkey brain emulsion believed to contain poliomyelitis virus without apparent effect, and on March 6 received a second subdural inoculation of the same material, following which it died March 10. Post-mortem examination showed no gross changes except an abscess in the right cerebral hemisphere, which apparently was the cause of death. Sections from the liver, kidney, spleen, and intestine were studied carefully microscopically, but no changes which could be ascribed to carbon tetrachloride were found.

Monkey No. 3 received 3 c. c. of carbon tetrachloride on February 23, 27, March 3 and 6, in addition to the doses mentioned above, or a total of 48 c. c. during a period of about six weeks. On March 6 this monkey received some of the suspected poliomyelitis virus subdurally and died on March 17. As in the case of monkey No. 4, careful examination of the organs, both grossly and microscopically, failed to show any changes ascribable to carbon tetrachloride, the cause of death being brain abscess.

Monkeys No. 1 and No. 2 received, in addition to the doses mentioned previously, 1 and 2 c. c., respectively, on February 23, 27, March 3 and 6, after which the treatment was discontinued.

Throughout the treatment with the carbon tetrachloride none of the monkeys showed any symptoms of intoxication. They ate well and appeared to be in good health. We endeavored to give the drug on an empty stomach. They were kept under observation until April 11, when they were released for other experiments, being apparently in good condition.

² Allen, J. A.: The efficiency of carbon tetrachloride against hookworms in the silver black fox. *Jour. Am. Vet. Med. Assn.*, N. S. vol. 14, No. 1, pp. 31-37.

The only points worth mentioning are that monkey No. 3 occasionally gagged on the passage of the stomach tube, but apparently more from the tube itself than from the drug. He was observed to vomit a small amount of material on two occasions, when he had accidentally been fed a few hours before the treatment. No difficulty whatever was experienced in dosing the other three monkeys, and none of them was ever observed to vomit. Monkey No. 4, during the second and third week of the experiment, passed a much larger quantity of feces than was normal, probably two to three times as much as the other monkeys; they contained a great deal of undigested food and were somewhat frothy at times. During the remainder of the experiment the feces of this animal were again practically normal.

Referring again to Hall's article, the indicated dose of the drug for man is the same as for the average-sized dog (10 kilos), viz, 3 c. c.; this is equivalent to 0.05 c. c. per kilogram for man. On this basis monkey No. 1, receiving the smallest dose given at each treatment, received more than ten times the amount per kilogram indicated for man, and this dose was repeated sixteen times within a period of 6 weeks. Monkey No. 4, receiving the highest dosage given in each treatment, received forty times the indicated dose per kilogram as compared with man, and this dose was repeated twelve times within a period of 30 days. The other two monkeys received doses between these extremes.

In view of the unusually promising results of carbon tetrachloride as an anthelmintic for hookworms in dogs, and dogs have always served as the experimental animal in studying the effects of other anthelmintics, especially thymol and chenopodium, and in view of the *unusually* low toxicity of the drug for monkeys, both when given in single and in repeated doses, the use of carbon tetrachloride in the treatment of hookworm in man is worthy of an extensive trial.

This opinion seems to be further warranted, in view of the fact that it is now conceded by all authorities on the subject that the use of thymol and chenopodium has not been without accidents, a number of fatalities being charged to each.

In man the drug should be given in hard gelatin capsules, the patient having fasted overnight, and should not be accompanied with castor oil. In fact no purgative, either at the time of administration or later, seems to be necessary, as the drug itself tends to increase peristalsis. The logical procedure would be to begin with the dose of 3 c. c. for the average patient, and, if the dosage seems too small, to increase it. It would appear safe to give as much as 10 c. c.

Caution.—Care must be taken to see that the capsules are swallowed promptly. Should one open in the mouth or throat and some of the drug enter the trachea, serious results might follow.

The only reference to the use of carbon tetrachloride for the treatment of hookworm disease in man that the writer can cite is in a

report in the *Lancet* ³ to the effect that in Suva, Fiji, coolies suffering from ankylostomiasis have been treated with carbon tetrachloride, and that 98 per cent of the worms were removed by a single dose, almost without symptoms.

SUMMARY AND CONCLUSION.

1. Four monkeys received carbon tetrachloride by stomach tube in amounts of 1, 2, 3, and 5 c. c., respectively, at intervals of 2 to 3 days, over a period of from 30 to 41 days, the total number of doses varying from 12 to 16.

2. No symptoms of importance were shown by the monkeys during this period.

3. The two monkeys receiving the larger doses were subsequently used for the testing of suspected poliomyelitis virus and died of brain abscess. In each case gross and microscopic examination of the important organs failed to show any changes indicative of an exogenous poisoning.

4. The doses received by the monkeys at each treatment were from 10 to 40 times greater in cubic centimeters per kilogram of body weight than the dose mentioned by Hall as that indicated for man, and these doses were repeated from 12 to 16 times.

From the data at hand, we must conclude that carbon tetrachloride by stomach has a very low toxicity for monkeys and that it is probable that man may safely be given considerably higher doses than the ones suggested by Hall; and that it might be safe to repeat the dosage several times at proper intervals (one week).

Finally, in view of the unusually promising results that carbon tetrachloride has given as an anthelmintic for hookworms in animals, and in view of its unusually low toxicity for animals, including monkeys, when given by stomach, both in single and in repeated doses, we believe that it deserves an extensive trial in the treatment of hookworm disease in man.

NOTE.—Hall has just informed the writer that he and Doctor Shillinger have given dogs as high as 300 c. c. as a single dose without causing evident toxic symptoms.

³ Carbon tetrachloride in ankylostomiasis. *The Lancet*, Vol. CCII, Feb. 25, 1922, p. 391.